HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	2
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Anticoagulant drugs

Recap

Last lecture we were talking about *antiplatelet drugs*, we mentioned 5 drugs : **Aspirin** which is used alone with patents that have high risk of coagulation or thrombosis, but if thrombosis actually occurs we will need to use a more aggressive treatment, which is; **Clopidogrel**; a prodrug that needs to be activated by CYP2C19, furthermore if the patient doesn't have CYP2C19 we must use an alternative drug; **Prasugrel**. We also have **Abciximab** which is used one hour or half an hour before angioplasty. Finally, **Dipyridamole** (not used in reality) it is added to aspirin or warfarin for its synergistic activity but might be seen as a dilator in pulmonary hypertension.

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*Today we are going to talk about **anticoagulant** drugs(the first two):*

A) Heparin
B) Low-Molecular-Weight Heparins:
Enoxaparin, dalteparin, tenzaparin
C) Heparinoids:
Danaparoid.
D) Direct & specific thrombin inhibitors:
Hirudin (leech protein), lepiridun, bivalirudin, argatroban, melagatran.
E) Oral direct & specific thrombin inhibitors:
Ximelagatran, Dabigatran
F) Pentasaccharide specific Xa inhibitors:
Fondaparinux, Rivaroxaban, Apixaban.
F) Warfarin

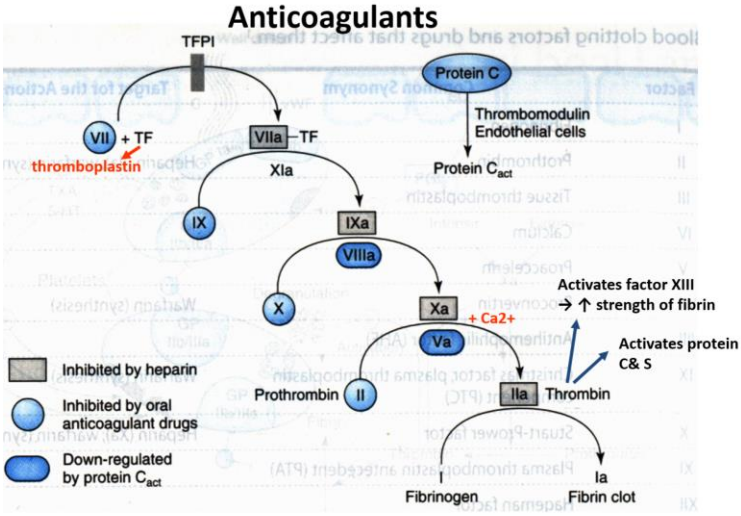
As you remember, coagulation cascade is the multiple steps that aim for the activation of fibrin, platelets and clotting factors (especially factor X)

The terminology for the pathways has changed; it used to be divided into Extrinsic and Intrinsic , but now it is Tissue activating and Non-Tissue activating. With that said, we will still be discussing subjects with perspective to extrinsic and intrinsic because in the labs, we have to ways; either to use the glass tube alone (intrinsic) or to add tissue factors (extrinsic)

The coagulation cascade ends with thrombin that activates fibrinogen to fibrin. We have anticoagulants that normally are found in our bodies *like protein C*

protein S ,prostaglandins ,platelet inhibitor factor, anti-thrombin III and heparin in mast cells.

You should know that what is inhibited by heparin is not inhibited by warfarin (oral anticoagulant) and vice versa as each one affects different clotting factors.



Half-life for <u>prothrombin (factor II) is 50 hrs</u>, <u>for factor VII is 6 hrs</u> and <u>for protein C is 6-10 hrs</u>.

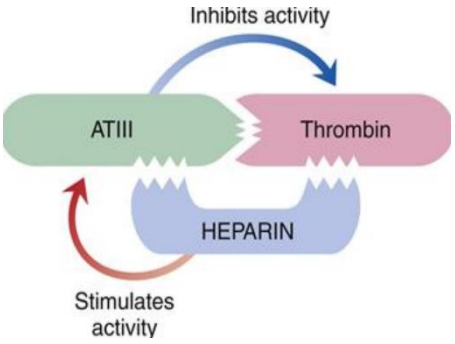
Warfarin and Thrombosis: warfarin affects prothrombin, factor XI, factor X, factor VII and protein C, which differ in their half-life, you will notice that the first side effect that will appear is thrombosis, why is that? Because protein C is the one with the least half life.

1)Heparin (UFH: unfractionated heparin)

An injectable drug, given for 5-7 days, fast and strong.

Most effective drug as anticoagulant but has a high chance to produce <u>*bleeding*</u>. It is a long polysaccharide (can be one monomer but different linkers), it is heterogeneous; varies from 30 K Dalton to 70 K Dalton, it is extracted from pigs and needs continuous monitoring for its complexity. So we started using the low molecular weight heparin (15 K Dalton/fractionated heparin /not heterogeneous) like Enoxaparin, trade name is *clexane*, we also have less used: dalteparin and tinzaparin. Clexane, successfully substituted heparin in 95% of the cases.

Heparin activates plasma protease inhibitor (***antithrombin III***) which is an endogenous anticoagulant in which its efficacy increases dramatically (from 1 to 1000) when heparin binds to it. **AT3** then inactivates XIIa, XIa, IXa, Xa and IIa(thrombin) so heparin must be composed of a long chain to work. This is why you will see LMWH having less effect on these factors since it is composed of a shorter chain (15 K Dalton).



We use Heparin to prevent further thrombus growth allowing the body's own thrombolytic system to dissolve clot, but it needs time to work (not used in cases of myocardial infraction) so we use it if the patient has unstable angina.

Heparin is used for:

- **DVT**(deep vein thrombosis) and **PE**(pulmonary embolism) *note: in general, thrombosis occurs in veins and embolism in arteries.

- **Afib** (atrial fibrillation) 160beats/min: to reduce the risk of thrombus formation and embolization. During Afib heart pumps clots instead of normal blood which will cause coagulation anywhere in the body.

- Cases of prosthetic valves **(exogenous)**, knee replacement since coagulation occurs, it is not enough to use the weak guys: antiplatelet; so we give heparin (affects fibrin, factor X)

Note: heparin is given in the hospital since it needs to be injected through infusion and has to be monitored every 6 hours through aPTT. Since it is not practical to give heparin for more than 5-7 days, we turn to the use of oral anticoagulant drugs, but why don't we use them from the beginning? Because we need something FAST which is injectable heparin.

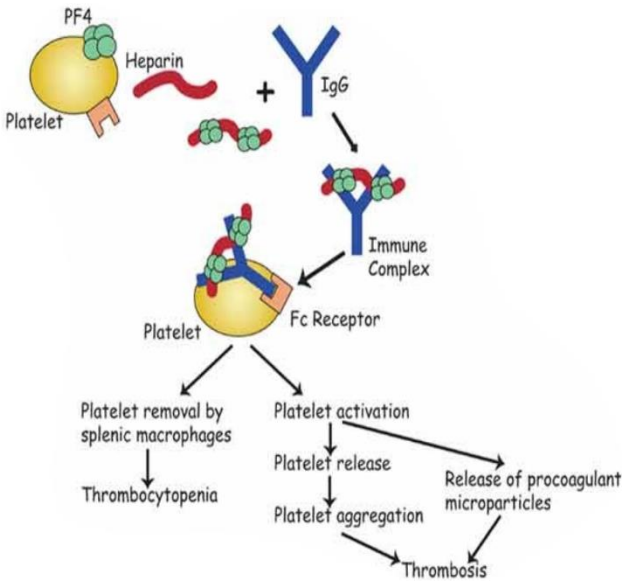
Laboratory Monitoring for UFH

-Activated partial thromboplastin time (aPTT): a blood test that measures the time it takes your blood to clot. Normally it is 24-36 seconds. An aPTT ratio (patient aPTT/control aPTT) of 2-2.5 should be **achieved** throughout infusion or 6 hours after intermittent administration, so it would take more time for the blood to clot, with a side effect of bleeding.

Side effects:

1-The major adverse effect is bleeding : it is a pharmacological side effect, for example with aPTT more than 4; bleeding occurs, but it can also occur even within the therapeutic aPTT (due to its effect on platelets, vascular permeability and even on beneficial clots.)

2-Heparin induced thrombocytopenia (HIT): it is an idiosyncratic side effect (you can't expect it) heparin binds to PF4 (platelet factor 4) causing allergic reaction inside the platelet which causes the immune system to attack the platelets and decrease their number to half *(thrombocytopenia)* and the vesicles that were inside platelets will be released to circulation causing *thrombosis and even ischemia* anywhere in the body which may lead to death. That is why you should do platelet count test at days 0,3 and 5 in order to see if there is a decline in platelets count, if there was, you stop heparin!



3-Heparin is of animal origin(pigs) and should be used cautiously in patients with allergy.

4-Increased loss of hair (reversible alopecia) in the long run.

5-Long-term heparin therapy causes osteoporosis.

6-Hyperkalemia (decreases aldosterone).

2)Low molecular Wight heparin (LMWHs)

Enoxaparin, dalteparin, tinzaparin & ardeparin are fragments of heparin.

Similar to heparin , they possess a unique pentasaccharide sequence in order to bind to and catalyze ATIII(antithrombin). Moreover, since it has a LMW which means it is shorter, it will oppose heparin and will preferentially inactivate factor Xa and minimally affect thrombin. Now, since LMWH minimally affects thrombin they will have a minimal impact on aPTT (most sensitive to thrombin) so we don't need monitoring while using LMWH, which is an advantage.

In *95% of the cases, the efficacy provided by the LMWHs is enough* to replace heparin. However, in *5% of cases we really need full heparin*, such as in open heart surgeries.

Exception for laboratory monitoring: in some cases like renal failure, pregnancy and obesity, you should monitor blood concentration of LMWH, because you cannot predict the response.

Enoxaparin: from same sources as regular heparin (mg).

Eliminated renally (monitor the patient with renal failure)but heparin is excreted with bile

Higher costs for these agents may be outweighed by earlier discharge from the hospital due to dosing convenience. Neutralization by protamine is incomplete.

Heparin and LMWH cannot be used for more than 5-7 days so we need to turn to the use of oral drug (warfarin) that inhibits function of vitamin K which inhibits coagulation factor (it will be taken with heparin).

*NOTE: Frequently asked USMLE question; your patient has kidney failure and is being treated with full heparin, do you have to adjust towards the creatinine clearance? No, because heparin is excreted through the bile, while LMWHs (15 K Dalton or less) is excreted through the kidney.

Advantages of LMWHs over Heparin

Ease of dosing and administration (SQ), once-twice daily injections, increase predictability of response, decrease the requirement of laboratory monitoring and hospitalization ,decrease risk of thrombocytopenia and osteoporosis (but generally you have to monitor the platelets as sometimes LMWH causes thrombocytopenia).

ADR of LMWHs:

-Reactions at the injection site: irritation, pain, hematoma, bruising and redness.

-Bleeding.

-HIT: platelets should be measured at baseline & between days 3 and 5 of therapy.